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Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepines via Reductive Cyclization of ω-Azido Carbonyl Compounds by TMSI: An Efficient Preparation of Antibiotic DC-81 and its Dimers†

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Abstract—ω-Azido carbonyl compounds on reaction with trimethylsilyl iodide (in situ prepared from TMSCl/NaI) led to the formation of diazepine imines in good yields under mild conditions. This methodology has been applied to the parent unsubstituted pyrrolobenzodiazepine, the natural product DC-81 and its dimers.

In recent years, there has been considerable interest in ring systems such as pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) that can recognise and bind to specific sequences of DNA.[1–3] These compounds have been obtained naturally from *Streptomyces* species and have been synthesized with structural modifications for improvement in sequence specific binding. These molecules exert the biological activity by covalently binding to the N2 of guanine in the minor groove of DNA through the imine or imine equivalent functionality at N10–C11 of the PBD ring system and thus interfere with DNA function. Most of the molecules interact with DNA in a sequence-selective manner and as such have potential as anti-tumour agents and gene targeting drugs.[4,5] In the last few years, various strategies.[6–20] have been proposed for the synthesis of these antibiotics and have met with varying degrees of success having different limitations.[21] It has been found that the introduction of the imine at N10–C11 position has usually given problems because of the reactivity of these functional groups.

We have earlier shown the reduction of azide to amines employing TMSCl/NaI.[22] This prompted us to study the reaction of trimethylsilyl iodide (TMSI) with ω-azido carbonyl compounds for the formation of the diazepine ring system. Therefore, this procedure has been illustrated by employing it for the DNA binding PBD antibiotics. The precursors methyl-(2*S*)-*N*-(2-azidobenzoyl)-pyrrolidine-2-carboxylates (**1**) have been prepared by literature method.[23]

The treatment of **1** with TMSCl/NaI (in situ preparation of TMSI) gave pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**3a**–**d**), in 80–85% yields. These dilactams have been employed as intermediates for the synthesis of naturally occurring PBD imines.[24–26] Whereas, the reduction of **1** with DIBAL-H gives the corresponding (2*S*)-*N*-(2-azidobenzoyl)pyrrolidine-2-carboxaldehydes (**2**) and this upon reaction with TMSCl/NaI at room temperature led to PBD imines (**4a**–**d**) in 70–75% yields (Scheme 1).[27]

The usefulness of this methodology has not only been demonstrated for DC-81 (**4c**), but also for the synthesis of the dimers of DC-81. Recently, DC-81 dimers linked through their C-8 position have been investigated as bis functional alkylating agents capable of cross-linking DNA.[28] These dimers are highly toxic for human cell lines with a preference for six base pair sequences.[29] In view of the biological importance of these PBD dimers[30] and our investigations in the design and synthesis of structurally modified PBD analogues[31–33] it has been considered of interest to explore a versatile synthetic strategy for the DC-81 dimers. It is envisaged that the azido reductive approach is a potential method of practical significance. In the present methodology DC-81 dimers have been prepared starting from bis[2-methoxy-4-(methoxy carbonyl)-5-nitrophenoxy] alkanes[34] (**5a**–**c**).

The reduction of **5a**–**c** followed by diazotization and hydrolysis gave the corresponding azido acids (**6a**–**c**). Coupling of azido acids with L-proline followed by esterification afforded the bis amides (**7a**–**c**). This upon reaction with TMSCl/NaI gave the corresponding PBD

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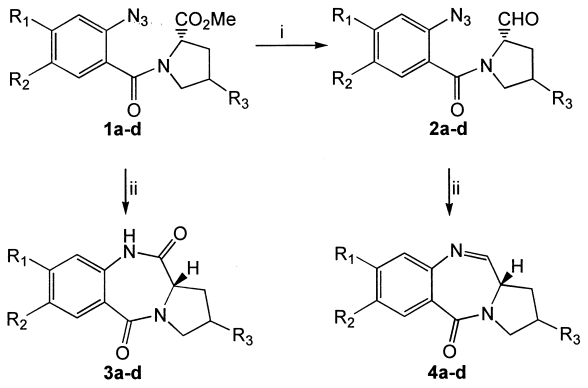
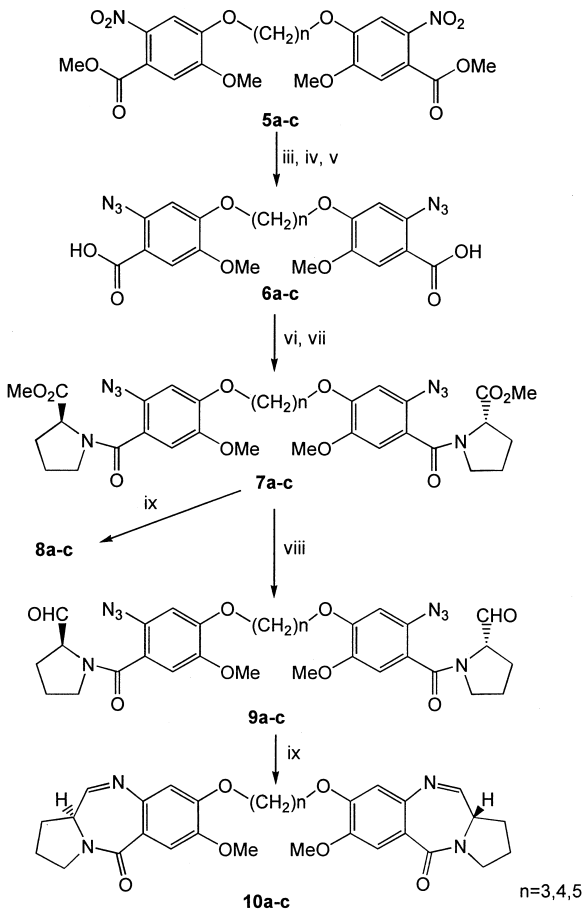
dimer dilactams (**8a**–**c**) in 50–55% yields. Whereas, reduction of ester functionality with DIBAL-H gives the corresponding azido carboxaldehydes (**9a**–**c**) and finally reductive cyclization with TMSCl/NaI at room temperature affords the DC-81 dimers (**10a**–**c**) in 40–45% yields (Scheme 2).[35] This is for the first time an efficient synthesis of C-8 linked pyrrolobenzodiazepine imines via an azido reductive approach has been developed.



Scheme 1. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78 °C, 45 min; (ii) TMSCl/NaI, MeCN, rt, 45 min.



Scheme 2. Reagents and conditions: (i) $SnCl_4/HNO_3$, CH_2Cl_2, −25 °C, 5 min; (ii) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, CH_2Cl_2, 0–5 °C, 30 min; (iii) $NaNO_2$, H_2SO_4/H_2O, 0 °C, NaN_3; (iv) 2 N NaOH; (v) $SOCl_2$, C_6H_6, 3 h, 2(S)-proline, THF, Et_3N, H_2O, 1 h; (vi) $SOCl_2$, C_6H_6, MeOH; (vii) DIBAL-H, −78 °C, CH_2Cl_2, 45 min; (viii) TMSCl/NaI, MeCN, rt, 45 min.

In conclusion, an efficient azido reductive cyclization process employing TMSCl/NaI (in situ preparation of TMSI) towards the synthesis of PBD dilactams and DNA interactive PBD imines under mild conditions has been demonstrated. Furthermore, this methodology has also been extended for the synthesis of DNA interstrand cross-linking PBD dimers in their imine (DC-81 dimers) and dilactam forms.

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27. Typical procedure for the synthesis of **4a**: To a stirred solution of **2a** (244 mg, 1 mmol) in acetonitrile (10 mL) NaI (298 mg, 2 mmol) was added under N_2 atmosphere at room temperature. After stirring for 5 min. trimethylsilyl chloride (217 mg, 2 mmol) in acetonitrile (3 mL) was added at same temperature and the stirring was continued for 45 min. After completion of the reaction indicated by TLC, ethyl acetate (20 mL) was added and the reaction mixture was washed with 10% sodium thiosulphate. The organic layer was dried over sodium sulphate, evaporated under reduced pressure and then purified by column chromatography on silica gel (chloroform:methanol 9.8:0.2) as eluent to give the pure compound **4a** in 75% yield. ^{1}H NMR ($CDCl_3$): δ 1.56–2.48 (m, 4H), 3.20–3.89 (m, 3H), 7.10–7.59 (m, 3H), 7.66 (d, 1H, $J = 4.2$ Hz), 8.02 (d, 1H, $J = 5.8$ Hz); IR ($CHCl_3$): 3300, 2975, 2875, 1615, 1570, 1480, 1240, 1165, 860, 830 cm^{-1}; MS: *m*/*e* 200 (M^+100).
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35. Typical procedure for the synthesis of **10a**: To a stirred solution of **9a** (310 mg, 0.5 mmol) in acetonitrile (10 mL) NaI (298 mg, 2 mmol) was added under N_2 atmosphere at room temperature. After stirring for 5 min. trimethylsilyl chloride (217 mg, 2 mmol) in acetonitrile (3 mL) was added at same temperature and the stirring was continued for 45 min. After completion of the reaction indicated by TLC, ethyl acetate (20 mL) was added and the reaction mixture was washed with 10% sodium thiosulphate. The organic layer was dried over sodium sulphate and evaporated under reduced pressure. Purification of the crude material by column chromatography on silica gel using chloroform and methanol (1:9) as eluent gave the pure compound **10a** in 45% yield. ^{1}H NMR: 1.95–2.15 (m, 4H); 2.25 (m, 6H); 3.45–3.85 (m, 6H); 3.89 (s, 6H); 4.15–4.28 (t, 4H); 6.78 (s, 2H); 7.42 (s, 2H); 7.60 (d, 2H); MS (FAB): 533 ($M + H^+$).